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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WANG, CHANG YU	
ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,144	BRIEND ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5/29/07.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,3-5,16,17,30,33,36,42,47,49-51,53-57,60,61,65,100 and 101 is/are pending in the application.

4a) Of the above claim(s) 12, 14, 37, 66 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,3-5,16,17,30,33,36,42,47,49-51,53-57,60,61,65,100 and 101 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) See Continuation Sheet are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 1,3-5,16,17,30,33,36,42,47,49-51,53-57,60,61,65,100 and 101.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed May 29, 2007 is acknowledged. Claims 2, 6-11, 13, 15, 18-29, 31, 32, 34, 35, 38-41, 43-46, 48, 52, 58, 59, 62-64, 67-99 are cancelled. Claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, 100 and 101 are pending in this application. Claims 12, 14, 37, 66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

2. Claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, 100 and 101 are under examination in light of compounds, in vivo, down-regulate/inhibitor, small molecule in this office action.

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

4. Applicant's arguments filed on May 29, 2007 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

5. The rejection of claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and 97-100 under 35 U.S.C. 112, second paragraph, for omitting essential steps is withdrawn in response to Applicants' amendment to the claims by reciting "exposing to a regulatory CD4+ T cell to a modulator" and cancellation

of claims 2, 6, 7, 11, 15, 18-22, 24, 25, 27, 29, 31, 34, 38, 39, 41, 43-46, 62-64, 67, 68, 97-99 and 100.

The rejection of claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and 97-101 under 35 U.S.C. 112, second paragraph, for being indefinite because of the recitations of "modulating/modulator/modified", "agonist" and "Notch signaling pathway" is withdrawn in response to Applicant's amendment to the claims by reciting a specific inhibitor and cancellation of claims 2, 6, 7, 11, 15, 18-22, 24, 25, 27, 29, 31, 34, 38, 39, 41, 43-46, 62-64, 67, 68, 97-99 and 100.

The rejection of claims 2, 6, 7, 11, 15, 18-22, 24, 25, 27, 29, 31, 34, 38, 39, 41, 43-46, 62-64, 67, 68, 97-99 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8, 10, 12, 14-16 of copending Application No. 10/765727 ('727), claims 16-32, 61-70, 72 of copending Application No. 10/846989 ('989), claims 28-61, 86, 100-119 of copending Application No. 10/845834 ('834), claims 1-16 of copending Application No.10/899422 ('422), claims 24-33 of copending Application No. 10/958784 ('784), claims 17-20 of copending Application No.11/058066 ('066), claims 1-20 of copending Application No. 11/178724 ('724), claims 1-7 of copending Application No.11/071796 ('796), claims 65, 68-73 of copending Application No. 11/232404 ('404), claims 4-6 of copending Application No. 11/231494 ('494), and claims 20-41 of copending Application No. 11/495015 ('015) is moot because the claims are canceled.

The rejection of claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and 97-101 under 35 U.S.C. 103(a) for being

unpatentable over US Patent No. 6887475 (issued May 3, 2005, filed May 4, 1999, priority date Nov 6, 1997) and Hadland et al. (PNAS, 2001. June 19. 98: 7487-7491) in view of Strooper et al. (Nature. 1999. 398:518-5522 as in IDS) is withdrawn in response to Applicants' cancellation of claims 2, 6-11, 15, 18-22, 24, 25, 27, 28, 30, 31, 34, 38, 39, 41, 43-46, 52, 62-64, 67, 68, 97-99 and Applicants' argument that US Patent No. 6887475 and the instant application were commonly owned (p. 8-9 of the response).

Claim Rejections/Objections Maintained

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, 100 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the Notch signaling induced by Delta-1 (a Notch ligand) in C2C12 cells and Jurkat-N2 cells with MW167, and enabling for inhibiting the production of notch-mediated cytokines by measuring decreased IL-10 and increased IL-5 in human CD4+ T cells isolated from peripheral blood in vitro, does not reasonably provide enablement for a method for decreasing regulatory CD4+ T cell activity by a structurally undefined inhibitor of presenilin or of presenilin-dependent gamma-secretase as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention

commensurate in scope with these claims. The rejection is maintained for the reasons made of record in Paper No.06062006, and as follows.

Applicants show that Delta (the Notch ligand) induces increased production of IL-10 and decreased production of IL-5 in human $CD4^+$ T cells and the effects of Delta can be reversed by MW167. Applicants also show that the Notch signaling can be inhibited by MW167 in Jurkat-N2 cells.

Applicant argues that amended claims are enabled because amended claims now recite "decreasing activation of regulatory CD4+ T cells by an inhibitor of presenilin or of presenilin-dependent gamma-secretase". Applicant's arguments have been fully considered but they are not persuasive.

In contrast to Applicants' assertion, the specification fails to provide sufficient guidance as to enable one of skill in the art to practice the full scope of the invention. Although several inhibitors of presenilin or presenilin-dependent gamma secretase are known in the art, the recitation of inhibitors of presenilin or presenilin-dependent gamma secretase encompass almost any agent, including those yet to be discovered. Accordingly, the court in *Genentech, Inc., v. Novo Nordisk*, 42 USPQ2d 1001, 1005 (1997), held that "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable", and that "reasonable detail must be provided in order to enable members of the public to understand and carry out the invention". The recitation of "inhibitors of presenilin or presenilin-dependent gamma secretase" is analogous to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in *In re Hyatt,* 708F.2d

712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "inhibitors of presenilin or presenilin-dependent gamma secretase" is that it covers any conceivable means, i.e. any molecules, compounds etc, which achieves the stated biological result while the specification discloses, at most, only a specific DNA [product] segment known to the inventor. Clearly the disclosure is *not commensurate in scope with the claim*s [emphasis added]. See *Ex parte Maizel* (27 USPQ2d 1662 at 1665).

Thus, in that no structure and little functional language (i.e., "inhibitors of presenilin or presenilin-dependent gamma secretase") are recited in the claims, and because the claims encompass using any product, the claims are not enabled, consistent with the above cited court decisions.

In addition, Applicants fail to teach what common structure/characteristics are required for the agent that down-regulates the Notch signaling as recited in claim 5. Therefore, a skilled artisan would not know how to make the components required to practice the currently claimed method because the structural and functional correlation between the claimed agent and the claimed invention is undefined, and thus unknown. Further, Applicants fail to teach what specific antigen or antigen determinant as recited in claims 16-17 can be used in the claimed methods. Although Notch has been shown to be involved in tumorgenesis and immune tolerance, without guidance of specific antigens or antigen determinants, a skilled artisan cannot contemplate how to use the claimed invention since no define antigen or antigen determinant is provided.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the

changes which can be made and still maintain activity is unpredictable and the experimentation left to those skilled in the art is extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed invention as currently claimed without further undue experimentation. Accordingly, the rejection of claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, 100 under 35 U.S.C. §112, first paragraph, because the specification does not enable the invention in scope commensurate with the claims is maintained.

7. Claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, 100 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons made of record in Paper No.06062006 and as follows.

Applicant argues that amended claims recite inhibitors of presenilin or presenilin-dependent gamma secretase of which Applicants have possession and several inhibitors are known in the art. Applicant's arguments have been fully considered but they are not persuasive.

In response, although several inhibitors are known in the art and the specification describes MK167 with formula I, Applicants fail to demonstrate possession of the genus

of inhibitors that can be used in the claimed method. Applicant also fails to demonstrate the genus of agent that can down-regulates the Notch signaling as recited in claim 5.

Accordingly, the court held in *Univ. California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) that:

"One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is".

and that:

"An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle &Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004)."

In contrast, an invitation for others to discover a representative number of species, or to discover what constitutes any particular portion of the structure that must be conserved, with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics has not reasonably been provided within the instant specification. Thus, Applicants were not reasonably in possession of the "claimed genus of inhibitors" and "the genus of agents that downregulate the Notch signaling", and for the reasons previously made of record. See again MPEP 2163. Therefore, the rejection of claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, 100 under 35 U.S.C.§ 112, first paragraph, for failing to meet the written description is maintained.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 101 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is maintained for the reasons made of record in Paper No.06062006, and as follows.

Applicants argue that amended claim 101 is not indefinite because it recites the chemical formula of "MW167". Applicants' argument has been fully considered but it is not persuasive. Although the specification describes formula I, the claim does not recite its precise structure, which renders the claim indefinite. Thus, the rejection is maintained. The rejection can be obviated by amending the claim to specifically and uniquely identify MW167, for example, by a precise structure and a specific function of MW167.

Obviousness-Type Non-Statutory Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, 100 and 101 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8, 10, 12, 14-16 of copending Application No. 10/765727 ('727), claims 16-32, 61-70, 72 of copending Application No. 10/846989 ('989), claims 28-61, 86, 100-119 of copending Application No. 10/845834 ('834), claims 1-16 of copending Application No.10/899422 ('422), claims 24-33 of copending Application No. 10/958784 ('784), claims 17-20 of copending Application No.11/058066 ('066), claims 1-20 of copending Application No. 11/178724 ('724), claims 1-7 of copending Application No.11/071796 ('796), claims 65, 68-73 of copending Application No. 11/232404 ('404), claims 4-6 of copending Application No. 11/231494 ('494), and claims 20-41 of copending Application No. 11/495015 ('015). The rejection is maintained for the reasons made of record in Paper No.06062006, and as follows.

Applicants request that the rejections be held in abeyance until conflicting claims are patented. Applicants' argument has been fully considered but it is not persuasive. The rejection of claims under obviousness double patenting for being unpatentable over the claims of copending Application Nos. 10/765727,10/846989, 10/845834, 10/899422,

10/958784, 11/058066, 11/178724, 11/071796, 11/232404, 11/231494, and 11/495015 is maintained of record until a terminal disclaimer is filed.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3-5, 30, 33, 42, 47, 49-51, 53-57, 60, 61, 100 are rejected under 35 U.S.C. 102 (b) as being anticipated by Doerfler et al. (PNAS, 2001. Jul 31. 98: 9312-9317).

Doerfler et al. teach a method of decreasing regulatory $CD4^+$ T cells activity by an inhibitor of presenilin-dependent gamma-secretase such as compounds 1 & 2 (L-685, 458) (i.e. as it relates to claims 1, 3 and 4; see p. 9313, 2nd col., 2nd paragraph; p. 9314, 2nd col., 2nd paragraph to p. 9315, 1st col.). Doerfler et al. teach that presenilin-γ-secretase inhibitors, compounds 1-3, which bind to presenilin-1 and -2 (i.e. synthetic, low molecular weight organic compounds as it relates to claims 3-4; p. 9313, 2nd col. 2nd paragraph), block the T cell development by inactivation of Notch-1 in fetal thymic organ cultures (i.e. as it relates to claims 4-5, 100; see p. 9314, 2nd col.). Although Doerfler et al. do not explicitly teach $CD4^+$ regulatory T cells, as previously made of record, the decrease of $CD4^+$ regulatory T cells (i.e. as it relates to claims 1, 30, 33) and modulation

of cytokine expression in regulatory $CD4^+$ T cells are inherent results of inhibiting Notch-1 signaling by an inhibitor of presenilin (PS-1 and PS-2) or presenilin-gamma secretase because activation of the Notch signaling pathway has effects on regulatory T cells and expression of cytokines and thereby modulates maturation of $CD4^+$ or $CD8^+$ T cells as evidenced by Hoyne et al. (i.e. as it relates to claims 1, 5, 30, 33, 42; see p. 219, Immunol. Rev. 2001. 182: 215-227, as in IDS, also see p.8 of the previous office action). Inhibition of the Notch signaling pathway by presenilin-γ-secretase inhibitors, compounds 1-3, in thymus organ cultures (containing T cells) as taught by Doerfler et al. would inherently result in decreasing $CD4^+$ regulatory cells (claim 1) including Tr1 regulatory T cells (claim 30) and Th3 regulatory T cells (claim 33), and would also inherently result in decreasing the expression of IL-10 or IL-4 (claims 47, 49-50, 60) and increasing IL-2, IL-5, TNF-a, IFN-g and IL-13 (claims 51, 53-57, 60, 61) as evidenced by Hoyne et al. (i.e. as it relates to claims 1, 5, 30, 33, 42; see p. 219, Immunol. Rev. 2001. 182: 215-227, as in IDS, also see p.8 of the previous office action).

Hoyne et al. teach that activation of the Notch signaling pathway has effects on regulatory T cells and expression of cytokines and thereby modulate maturation of $CD4^+$ or $CD8^+$ T cells. Hoyne et al. also teach that $CD4^+$ T cells include Th1 cells, Th2 cells and $T_{regulatory}$ (Tr) cells. Hoyne et al. teach that the changes of different subsets of T cells and cytokines are natural processes of the immune response because regulatory T cells include $CD4^+CD25^+$ T regulatory cells, IL-1-secreting Tr1 cells and Th3 cells, and different cytokine expression can be mediated by these different T cells. In addition, the expression of different cytokines also affects different subsets of T cells and these

interactions are coordinative with each other. For example, Tr cells secrete inhibitory cytokines such as IL-10 and TGF-β1 (i.e. as it relates to claims 42, 47, 49-51, 61); IL-4 directs $CD4^+$ T cells to differentiate to Th2 cells that are effective in promoting humoral immunity; IL-10 promotes the differentiation of $CD4^+$ T cells into regulatory T (Tr) cells to suppress an immune response; and Th1 cells secrete IL-2, IFN-γ, TNF-α and lymphotoxin-β and Th2 cells secrete IL-4, IL-5, IL-9 and IL-13 (i.e. as it relates to claims 49-51, 53-57). Thus, the changes of subsets of $CD4^+$ T cells and cytokines are inherent results in response to an antigen or a combination of antigen with an inhibitor of the Notch signaling pathway in vitro or in the immune system in vivo because the responses of T cells and cytokines as well as the properties/features of different T cells and cytokines are an natural immune response to administration of an inhibitor of Notch IC protease activity (i.e. as it relates to claims 30, 33, 42, 47, 49-51, 53-57, 60, 61).

It is noted that no active steps for subsets of $CD4^+$ T cells as recited in claims 30, 33 and for cytokines as recited in claims 42, 47, 49-51, 53-57, 60, 61. The recitations of the changes of the subsets of $CD4^+$ T cells and cytokines in these claims are the mechanisms of an immune response in response to an antigen or a combination of antigen with an inhibitor of the Notch signaling pathway in vitro or in the immune system in vivo. Independent claims 1 and 42 only recite "exposing a regulatory $CD4^+$ T cell to an inhibitor of presenilin or of presenilin-dependent gamma-secretase, which is taught by Doerfler. Thus, claims 1, 3-5, 30, 33, 42, 47, 49-51, 53-57, 60, 61, 100 are anticipated by Doerfler et al.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-5, 16, 17, 30, 33, 36, 42, 47, 49-51, 53-57, 60, 61, 65, 100 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doerfler et al. (PNAS, 2001. Jul 31. 98: 9312-9317) in view of Strooper et al. (Nature. 1999. 398:518-522 as in IDS, cited in the previous office action) and Lamb et al. (WO01/35990, published May 25, 2001, as in IDS).

Doerfler et al. is as set forth in paragraph 10. However, Doerfler et al. fail to teach that the presenilin-dependent γ-secretase inhibitor is a MW167 (i.e. as it relates to claim 101). Doerfler et al. also fail to teach an antigen (as it relates to claims 16 and 17) and administration of an inhibitor in vivo (claims 36 and 65).

Strooper et al. teach that several γ-secretase inhibitors, including MW167, are able to inhibit the processing of Notch1 to release Notch IC (i.e. as it relates to claims 1,

42, and 101see p. 520, 1st col., 1st paragraph to 2nd col., 2nd paragraph). Strooper et al. teach that Notch signaling requires ligand-induced cleavage. The cleavage occurs within the transmembrane domain of Notch to release the intracellular domain of Notch. The process of Notch cleavage is similar to the process of γ-secretase mediated cleavage of APP, which is regulated by presenilin-1 and -2 (p. 518, abstract). Presenilin deficiency reduces the proteolytic release of Notch IC as in claims 2, 3, 6, 7(p. 518, abstract). The teachings of Strooper et al. indicate that an inhibitor of Notch IC protease activity, such as MW 167, is an inhibitor of presenilin-1 or -2 or presenilin-dependent γ-secretase and can block the Notch signaling pathway (as it relates to claims 1, 3-5 and 101). However, Strooper et al. do not teach decreasing CD4+ regulatory T cells.

Lamb et al. (WO01/35990) teach methods of immunotherapy and cancer therapy by blocking the Notch signaling pathway (as it relates to claims 1 and 16-17; see p.21-23; p.30-31). Lamb (WO'990) teaches that in pathological conditions, such as tumor-induced immunosuppression or infections, immunosuppression is a common feature and it would be desirable to inhibit the T cell interactions passing on the infectious tolerance (p.2). Lamb (WO'990) also teaches that administration of Serrate/Delta (Notch ligands) prevents antigen priming of lymphocytes and normal T cell responses but induces regulatory T cell responses and induces immune tolerance (p.2-3). Lamb (WO'990) teaches treatment of cancer by vaccination or reintroduction of T cells, antigen presenting cells or tumor cells isolated from patients and treated with an agent that downregulates the expression of Notch and Notch ligands such as Serrate/Delta or decreases the interaction between Notch and Notch ligand to block the Notch signaling

pathway and enhance tumor-antigen recognition (i.e. as it relates to claims 16-17, 36 and 65; see p. 8-9; 21-23; 30-31). The teachings of Lamb (WO'990) provide a motivation to one of skill in the art to enhance the cellular immunity that regulates tumor or infection by inhibiting the Notch signaling pathway using an inhibitor of the Notch signaling pathway since activation of the Notch signaling pathway reduces T cell activation in allergy and immune tolerance and increases regulatory T cells. The teachings of Lamb (WO'990) also provide a motivation and expectation of success in using a combination of a tumor antigen with an inhibitor of presenilin or presenilin-γ-secretase to block the Notch signaling pathway that is involved in tumorgenesis and enhance tumor recognition. However, Lamb et al.(WO'990) fail to teach using an inhibitor of presenilin or presenilin-γ-secretase.

Thus, it would have been obvious to one of ordinary skill in the art to be motivated to downregulate the Notch signaling that is involved in tumorgenesis or infection by an inhibitor of presenilin or presenilin-γ-secretase or a combination of an inhibitor of presenilin or presenilin-γ-secretase with a tumor or pathogen antigen or antigen determinant to enhance a productive immunity against tumor or infection. The person of ordinary skill in the art would have been motivated to do so since the activation of the Notch signaling pathway is involved in tumorgenesis and immune tolerance. Thus, one of ordinary skill in the art would have expected success in downregulating regulatory T cells and decreasing production of IL-10 or IL-4 by inhibiting the Notch signaling pathway using an inhibitor of the Notch IC protease activity or using an inhibitor of presenilin or presenilin-γ-secretase since the abnormal

activation of the Notch signaling pathway is involved in tumorgenesis and blocking the Notch signaling would inhibit tumorgenesis. In addition, it would also have been obvious to one of ordinary skill in the art at the time the instant invention was made to be motivated and have expected success in using an inhibitor of Notch IC protease activity, such as MW 167, or in combination with a tumor or a pathogen antigen or antigen determinant, to decrease regulatory T cells, to decrease the expression of IL-10 or IL-4 and to increase the production of IL-5, and thereby to enhance the immunity against tumor and infection.

Conclusion

12. NO CLAIM IS ALLOWED.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

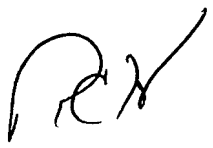
Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
July 18, 2007



ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER